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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,939	08/02/2007	Haruo Sugiyama	14875-168US1 C1-A0401P-US	9482

26161 7590 12/22/2011

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
12/22/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,939	SUGIYAMA ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *21,22,24,27,30,31,34-36,39,42,43 and 46-52* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *21,22,24,27,30,31,34-36,39,42,43 and 46-52* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/22/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on November 21, 2011 has been entered.

Claims 23, 25, 26, 28, 29, 32, 33, 37, 38, 40, 41, 44, and 45 have been canceled. Claims 21, 27, and 34 have been amended.

Claims 21, 22, 24, 27, 30, 31, 34-36, 39, 42, 43, and 46-52 are pending in the instant application.

Claims 21, 22, 24, 27, 30, 31, 34-36, 39, 42, 43, and 46-52 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Applicant's Amendment and Response filed November 21, 2011 have been considered. Rejections and/or objections not reiterated from the previous Office Action mailed October 26, 2010 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections

presently applied to the instant application.

Information Disclosure Statement

Applicant's information disclosure statement filed November 22, 2011 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed October 26, 2010, claims 23, 28, 29, 40, and 41 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection is moot** in view of Applicant's Amendment filed November 21, 2011 to cancel claims 23, 28, 29, 40, and 41.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed October 26, 2010, claims 21-25, 27, 30-32, 34-37, 39, 42-44, and 46-52 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,034,235 (provided as reference A1 on the Information Disclosure Statement filed August 4, 2008), in view of Hammond et al. (Nature Genetics 2001, Vol. 2:110-119, of record), and WO 03/061386 A1 (provided as reference #4 on the Information Disclosure Statement filed July 21, 2009). **This rejection is moot** against claims 23, 25, 32, 37, and 44 in view of Applicant's

Amendment filed November 21, 2011 to cancel these claims. **This rejection is maintained** against claims 21, 22, 24, 27, 30, 31, 34-36, 39, 42, 43, and 46-52 for the reasons of record as set forth in the previous Office Action mailed October 26, 2010.

Response to Arguments

In response to this rejection, Applicants contend that independent claim 21 is drawn to an siRNA molecule comprising a sense strand hybridized to an antisense strand, wherein the antisense strand targets a region in a 17AA site of a Wilms' tumor gene transcript, the siRNA suppresses cell growth, the sense strand comprises SEQ ID NO:1 and the antisense strand comprises SEQ ID NO:2; independent claim 27 is drawn to a DNA comprising a sequence that is transcribed into a sense RNA strand and an antisense RNA strand that hybridize together to form an siRNA that suppresses cell growth, wherein the antisense RNA strand targets a region in a 17AA site of a Wilms' tumor gene transcript, these sense strand comprises SEQ ID NO:1, and the antisense RNA strand comprises SEQ ID NO:2; and independent claim 34 is drawn to a pair of DNAs, the first DNA comprising a sequence that is transcribed into a sense RNA strand and the second DNA comprising a sequence that is transcribed into an antisense RNA strand, wherein the sense and the antisense RNA strands hybridize together to form an siRNA that suppresses cell growth, the antisense RNA strand targets a region in a 17AA site of a Wilms' tumor gene transcript, the sense RNA strand comprises SEQ ID NO:1, and the antisense RNA strand comprises SEQ ID NO:2.

Applicants argue that U.S. Patent No. 6,034,235 discloses the exon 5 sequence of WT1 as SEQ ID NO:14 and states than an antisense oligonucleotide derivative to the sequence may be used to suppress levels of WT1. Applicants acknowledge that SEQ ID NO:1 of Applicant's invention is contained within SEQ ID NO:14 of U.S. Patent No. 6,034,235.

Applicants argue that the Office Action alleges that there is expectation of success because U.S. Patent No. 6,034,235 teaches the successful use and design of an antisense molecule targeted to exon 5. Applicants contend that no such teaching exists in U.S. Patent No. 6,034,235 and request that the Examiner identify this alleged disclosure.

In reviewing U.S. Patent No. 6,034,235, it is determined that while the Patent does not explicitly teach the successful use and design of an antisense molecule targeted to exon 5, U.S. Patent No. 6,034,235 instead teaches the successful use and design of an antisense molecule targeted to exon 6. See, for example SEQ ID NO:15, column 2, lines 51-55, and Figures 1, 6, and 7. It is the Examiner's position that one of ordinary skill in the art could take the teachings and suggestions of U.S. Patent No. 6,034,235 as they relate to exon 6 and apply them accordingly and with a reasonable expectation of success to design and use an antisense molecule targeted to exon 5.

Furthermore, U.S. Patent No. 6,034,235 teaches antisense oligonucleotides complementary to a WT1 gene transcript (see Abstract and column 2, lines 10-62). Specifically, U.S. Patent No. 6,034,235 teach the antisense oligonucleotide derivatives used in the invention is an antisense oligonucleotide derivative to WT1, examples of

which include that to the transcription capping site of WT1 gene, that to the translation starting region, that to an exon or that to an intron. U.S. Patent No. 6,034,235 teaches SEQ ID NO:14 (exon 5), which, as Applicants acknowledge contains SEQ ID NO:1 of Applicant's invention. U.S. Patent No. 6,034,235 also teaches that the antisense oligonucleotides of their invention comprise 5 to 50 continuous nucleotides or 5 to 70 nucleotides of antisense DNA or RNA chain for WT1. U.S. Patent No. 6,034,235 also taught that antisense oligonucleotides complementary to a WT1 gene transcript were used to inhibit WT1 expression and suppresses cell growth in leukemia cell lines (see Figures, for example).

Applicants next argue that U.S. Patent No. 6,034,235 does not teach an actual antisense targeted to exon 5, but instead only shows that a hypothetical antisense molecule that targets SEQ ID NO:14 (exon 5) could suppress expression of WT1.

While it is noted that U.S. Patent No. 6,034,235 does not teach an actual antisense targeted to exon 5, it should be also be noted that the instant rejection is not a 35 U.S.C. § 102 rejection of anticipation. Instead, the instant rejection is a 35 U.S.C. § 103 rejection and the prior art references have been properly combined because there is a teaching, suggestion or motivation for their combination to provide the claimed invention.

As discussed *supra*, U.S. Patent No. 6,034,235 teaches the successful use and design of an antisense molecule targeted to exon 6. See, for example SEQ ID NO:15, column 2, lines 51-55, and Figures 1, 6, and 7. It is the Examiner's position that one of ordinary skill in the art could take the teachings and suggestions of U.S. Patent No.

6,034,235 as they relate to exon 6 and apply them accordingly and with a reasonable expectation of success to design and use an antisense molecule targeted to exon 5.

Applicants next argue that nothing in U.S. Patent No. 6,034,235, Hammond, and/or WO 03/061386 teaches that success with a particular antisense molecule is predictive of success with siRNA that targets the same sequence targeted by the antisense molecule. Instead, Applicants argue that the art of Davies et al. (Human Molecular Genetics, 2004 Vol. 13:235-246, provided on Applicant's Information Disclosure Statement filed November 22, 2011) and McManus et al. (J. Immunol., 2002 Vol. 169:5754-5760, provided on Applicant's Information Disclosure Statement filed November 22, 2011) teach the unpredictability of individual siRNAs and the unpredictability associated with the siRNA field. Based on this unpredictability, and the fact that U.S. Patent No. 6,034,235 did not demonstrate success even with an antisense molecule targeting SEQ ID NO:14, the ordinary artisan would not have had any reasonable expectation that an siRNA version of U.S. Patent No. 6,034,235's hypothetical antisense molecule targeting SEQ ID NO:14 would be able to suppress WT1 expression.

These arguments have been fully considered, but are not found persuasive because first, one of ordinary skill in the art would be able to reasonably expect success with a particular antisense molecule is predictive of success with siRNA that targets the same sequence targeted by the antisense molecule. For example, Vickers et al. (Journal of Biological Chemistry, 2003 Vol. 278: 7108-7118, Epub date 2002, Dec 23) teach siRNA oligonucleotide- and RNase H-dependent antisense strategies are both

valid strategies for evaluating function of genes in cell-based assays. Specifically, Vickers et al. teach that positions on target RNA identified as being susceptible for RNase H-mediated degradation would be coincident with siRNAs designed to bind the same position on the target mRNA as RNase H-dependent oligonucleotides (see Abstract and Table I).

Furthermore, based on the fact that U.S. Patent No. 6,034,235 teaches 1) how to design antisense oligonucleotides targeted to regions within the WT1 gene, including an exon region; 2) how to successfully use antisense oligonucleotides targeted to regions within the WT1 gene, including an exon region; and 3) SEQ ID NO:14 (exon 5) is a target region that can be targeted for antisense oligonucleotide design and for suppression of WT1, it is the Examiner's position that one of ordinary skill in the art can take these teachings and suggestions to arrive at Applicant's claimed invention.

While U.S. Patent No. 6,034,235 does not teach an siRNA molecule, Hammond was relied upon to teach that antisense and RNA interference are two methods of silencing expression of a gene and that RNA interference possesses characteristics that make it superior to antisense. Therefore, one of ordinary skill in the art would have been motivated to make the siRNA molecule comprising a sense strand hybridized to an antisense strand, wherein the antisense strand targets a region in a 17AA site of a Wilms' tumor gene transcript, and wherein the siRNA suppresses cell growth, the sense strand comprises SEQ ID NO:1 and the antisense strand comprises SEQ ID NO:2 of Applicant's claimed invention since U.S. Patent No. 6,034,235 taught the desire to make antisense molecules targeted to SEQ ID NO:14 (exon 5).

One of ordinary skill in the art would have been motivated to substitute the antisense molecule targeted to exon 5 taught and suggested by U.S. Patent No. 6,034,235 with a siRNA since it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06. Furthermore, one of ordinary skill in the art would have been motivated to substitute the antisense molecule targeted to exon 5 taught and suggested by U.S. Patent No. 6,034,235 with a siRNA since Hammond et al. taught that RNA interference is superior to antisense. Furthermore, Vickers et al. teach that one can make and use siRNAs comprising already known antisense oligonucleotide sequences.

One of ordinary skill in the art would have reasonably expected success at making the siRNA molecule comprising a sense strand hybridized to an antisense strand, wherein the antisense strand targets a region in a 17AA site of a Wilms' tumor gene transcript, and wherein the siRNA suppresses cell growth, the sense strand comprises SEQ ID NO:1 and the antisense strand comprises SEQ ID NO:2 of Applicant's claimed invention since U.S. Patent No. 6,034,235 taught the successful use and design of an antisense molecule targeted to an exon within the WT1 gene. U.S. Patent No. 6,034,235 also taught the design of both sense and antisense sequences of an exon of the WT1 gene and how to successfully use the antisense sequence to inhibit the cell growth of leukemia cells.

Thus, based on the fact that U.S. Patent No. 6,034,235 teaches how to design and use antisense oligonucleotides targeted to regions within the WT1 gene, including an exon region, and teaches that SEQ ID NO:14 (exon 5) is a target region that can be

targeted for antisense oligonucleotide design and for suppression of WT1, it is the Examiner's position that one of ordinary skill in the art can take these teachings and suggestions to arrive at Applicant's claimed invention.

It should also be noted that for obviousness under § 103, "all that is required is a reasonable expectation of success", and it does not require "absolute predictability of success". See *In re O 'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) at 1681. Note that U.S. Patent No. 6,034,235 teaches how to design and use antisense oligonucleotides targeted to regions within the WT1 gene, including an exon region. See exon 6. Thus, one of ordinary skill in the art can take the teachings and suggestions as they relate to exon 6 and reasonable apply them to arrive at designing and using an antisense oligonucleotide targeted to exon 5. Again, all that is required for 103 is a "reasonable" expectation of success.

Applicant has provided Davies et al. (*Human Molecular Genetics,* 2004, 13:235-246) and highlighted a passage in the reference stating that "the effectiveness of any particular siRNA is difficult to predict." It should be noted that the mere fact that predicting the effectiveness of siRNAs is difficult does not whatsoever indicate that making or synthesizing or producing the claimed invention would have been unpredictable at the time of filing. For further explanation, see the combined teachings of U.S. Patent No. 6,034,235 and Hammond et al. Also, see Vickers et al. Again, obviousness does not require an absolute expectation of success.

Applicant has also pointed out page 5757 of McManus et al., which teaches that the "majority" of siRNAs were not effective. Note that the instant ground of rejection is

based on the fact that U.S. Patent No. 6,034,235 teaches how to design and use antisense oligonucleotides targeted to regions within the WT1 gene, including an exon region and teaches that SEQ ID NO:14 (exon 5) is a target region that can be targeted for antisense oligonucleotide design and for suppression of WT1. Thus, is the Examiner's position that one of ordinary skill in the art can take the teachings and suggestions of U.S. Patent No. 6,034,235 as they relate to exon 6 and reasonably apply them to arrive at Applicant's claimed invention.

Furthermore, in contrast to the ineffective siRNAs synthesized by McManus et al., based on the teachings and suggestions of U.S. Patent No. 6,034,235, a person of ordinary skill in the art would not expect unpredictability in making and designing antisense oligonucleotides targeted to exon 5. Furthermore, a siRNA equivalent of an antisense targeted to exon 5 would have been reasonably expected based on the teachings of U.S. Patent No. 6,034,235 and Hammond et al. Also, see Vickers et al.

Applicants next argue that at the time of filing of the application, the art taught away from the claimed invention. Applicants point the Examiner to Yamagami et al. (of record) and Murata et al. (of record).

It is noted that neither Yamagami et al. nor Murata et al. have been relied upon in the instant rejection. Therefore, arguments discussing these references appear to be misplaced and will not be considered, addressed, or discussed by the Examiner.

Applicants next argue that U.S. Patent No. 6,034,235 itself teaches away from Applicant's claimed invention because U.S. Patent No. 6,034,235 focuses on targeting regions other than exon 5. Applicants point the Examiner to Figures 1, 6, and 7, where

antisense molecules that target the transcription capping site, capping region, or translation state site worked better at inhibiting cell growth than antisense targeted to exon 6. Applicants contend that of ordinary skill in the art upon reading U.S. Patent No. 6,034,235 would be motivated to use antisense molecules that target regions other than the exon regions.

These arguments and contentions have been fully considered, but are not found persuasive because first, U.S. Patent No. 6,034,235 explicitly teaches at column 2, lines 44-47:

> "Ten exons are contained in the region coding for WT1, and examples of the antisense oligonucleotide derivative of the present invention include those to the sequences contained in any of these exons"

Second, while the claims require that the siRNA suppresses cell growth, the clams do not require a specific level of cell growth suppression. Therefore, the fact that antisense molecules targeted to exon 6 suppressed cell growth, and to a high degree over control (see Figures 1, 6, and 7, AS4), one of ordinary skill in the art would be motivated to design and use antisense molecules that target exon regions, including exon 6 or exon 5, for example. See the teachings and suggestions of U.S. Patent No. 6,034,235.

In view of the foregoing, after consideration of all the evidence and facts, the totality of the rebuttal evidence of non-obviousness fails to outweigh the evidence of obviousness made of record. Thus, it is maintained that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

No claims are allowable at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 8 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Terra Cotta Gibbs/
December 15, 2011